REMARKS

Claims 1-48 are pending in the application prior to entry of amendments submitted herewith. All of Claims 1-48 stand rejected. By amendment herewith, Claims 1, 14, 18, 23, 35, 38, 46 and 47 are being changed. Specific issues raised in the August 28, 2001 Office Action are addressed below.

I. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-48 have been rejected under 35 U.S.C. §112, second paragraph. The Examiner specifically objected to certain text used in some of the Claims. The rejection is traversed.

In Claim 1, the Examiner objected to the presence of "too many open-ended terms." The undersigned is unaware of any limit as to the number of open-ended terms that can be included in a claim, and respectfully requests clarification from the Examiner as to how many are too many, why, and what legal authority there is too support such an assertion. Nevertheless, Claim 1 has been amended in an attempt to address the Examiner's concerns.

In Claim 1, the Examiner objected to the use of "system" in the terminology "cosolvent system", as rendering Claim 1 indefinite. The recited "cosolvent system" is not indefinite. As specifically provided in Claim1, the "cosolvent system" includes at least two different organic solvents. Moreover, the "cosolvent system" is thoroughly discussed in the application at, *inter alia*, page 4, line 9 through page 6, line8; page 11, line 20 through page 17, line 2; and page 19, line1 through page 22, line 14. Furthermore, in Merriam-Webster's Collegiate Dictionary, Tenth Edition (1999), the first definition provided for "system" is "a regularly interacting or interdependent group of items forming a unified whole." A copy of page 1197 of the dictionary including the quoted definition is enclosed. The "cosolvent system" includes multiple items (at least two organic solvents) that regularly interact (mutually soluble). The use of the term "system" in the recited "cosolvent system" is consistent with this ordinary dictionary meaning of "system."

The Examiner objected to the use of the terminology "first organic solvent" and "second organic solvent" as failing to distinguish one solvent over the other. Although it is believed that this is inherent in the claims as written and from use of the terminology in the description of the application, Claim 1 has, nevertheless, been amended to specifically recite that the first organic solvent and the second organic solvent are not the same. The Examiner also indicates that these

terms are used interchangeably in the claims, and as an example points to Claims 8 and 9 (second organic solvent is an alcohol) and claims 25, 26 and 27 (first organic solvent is an alcohol). There is no improper or confusing use in the claims of the terms first organic solvent and second organic solvent. Claims 8 and 9 and Claims 25-27 are simply directed to different embodiments of the claimed invention. Again the Examiner is directed to the portions of the description cited above, where it is amply discussed that there are different embodiments with respect to the cosolvent system, and that any particular organic solvent can serve as the first organic solvent in one embodiment and as the second organic solvent in another embodiment.

In Claim 14, the Examiner objected to the use of the term "amphiphillic materials" as rendering the claim indefinite. Such is not the case. Again referring to Merriam-Webster's Collegiate Dictionary, Tenth Edition (1999), the word "amphiphilic" is defined as "of or relating to, or being a compound (as a surfactant) consisting of molecules having a polar water soluble group attached to a water-insoluble hydrocarbon chain." A copy of page 39 of the noted dictionary is enclosed showing the quoted definition. Hawley's Condensed Chemical Dictionary, Twelfth Edition, defines "amphiphilic" as "molecule having a water-soluble polar head (hydrophilic) and a water-insoluble organic tail (hydrophobic)." A copy of page 72 from that dictionary is enclosed showing the quoted definition. Claim 14 has been amended to use the spelling "amphiphilic" consistent with that used in the two cited dictionaries. The spelling "amphiphillic" used in the application is clearly either a typographical error or a less common variation on the spelling of the word. Moreover, claim 14 places the term "amphiphilic material" in context as being a material that can improve solubility of the insulin through hydrophobic ion pairing. Hydrophobic ion pairing is a known technique for solubilizing insulin in nonpolar organic solvents, which technique is avoided in the embodiment of the invention recited in Claim 14. For a discussion on the use of amphiphilic materials to effect hydrophobic ion pairing for solubilizing insulin in nonpolar organic solvents, the Examiner is referred, for example, to U.S. Patent No. 5,770,559, a copy of which is enclosed for the Examiner's reference.

In Claim 35, the Examiner objected to use of the term "first" in line 1 of the claim and use of the term "dissolving the insulin in" in line 2 of the claim. Claim 35 has been amended consistent with the Examiner's suggestions.

The Examiner has objected to the use of the following relative terms as rendering the claims indefinite: "at least" (Claim 1), "more soluble"(Claim 2), "greater than" (Claims 3, 10,

39, 45), "less than" (Claim 5), "substantially" (Claim 14, 21 and 38), "larger than" or "greater than" (Claims 15, 46 and 47) and "at least a portion" (Claim 19). It is noted that the specific terms used in some of the identified claims do not match the terms noted by the Examiner. Nevertheless, the Examiners' position with respect to indefiniteness for simply using relative terms is disagreed with, regardless of the specific relative term that might be used in any given claim. Specifying in a claim that an element has a property with a value that bears some relationship to another known or determinable value is the antithesis of indefiniteness.

With respect to "at least", as used in Claim 1, the terminology clearly indicates that the presence of the first organic solvent and the second organic solvent are required in the cosolvent system, but that the presence of other organic solvents is not precluded, which is consistent with the disclosure (please refer to portions of the application description noted above concerning the cosolvent system). There is no indefiniteness.

With respect to "more soluble", as used in Claim 2, the terminology clearly indicates that, for the embodiment recited in that claim, the first and second organic solvents are such that the insulin is soluble to a greater degree in the first organic solvent than in the second organic solvent, which is consistent with the disclosure (please refer to portions of the description noted above concerning the cosolvent system). There is no indefiniteness.

With respect to "larger than" or "greater than", as used in Claims 3, 10, 15, 39, 46 and 47, the terminology clearly indicates that, for those recited embodiments, a certain claim element (volume ratio of first and second organic solvents in Claim 3, reduced pressure of compressed anti-solvent in Claim 10, opening for introduction of compressed anti-solvent fluid in Claim 15, reduced pressure of the compressed anti-solvent fluid in claim 39, and degree of encapsulation of insulin in Claims 46 and 47) is specified to exceed a definite value recited in the respective claim. There is no indefiniteness.

With respect to "smaller than" in Claim 5, the terminology clearly indicates that, for that recited embodiment, insulin is present in the cosolvent system at a concentration below a specific recited concentration value. There is no indefiniteness.

With respect to "at least a portion", as used in Claims 19, the terminology clearly indicates that some, but not necessarily all, of the insulin in the feed solution is in the form of colloidal particles. There is no indefiniteness.

With respect to "substantially", the term is clearly recognized as being a proper term, as specifically noted in MPEP §2173.05(b), subparagraph D. Nevertheless the term has been removed from the claims, even those claims in which the use of the term had not been objected to. It is noted that Claim 21 has never included the term.

In Claims 46 and 47, the Examiner objected to the use of the term "so that". The term has been removed from those claims.

The rejection of Claims 1-48 under 35 U.S.C. §112, second paragraph should be withdrawn.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1-48 have been rejected under 35 U.S.C. §112, first paragraph, based on an assertion of lack of an enabling disclosure. The rejection is traversed.

The Examiner has asserted lack of enablement with respect to the first and second organic solvents, the compressed antisolvent fluid, and separation of insulin-containing particles. All of these objected-to elements are recited in independent Claim 1. The Examiner also asserts lack of enablement with respect to criteria for making multi-component particles and the polymer. These elements are not recited in independent Claim 1, but are recited in dependent Claim 20, which specifically concerns making multi-component particles including insulin and a biocompatible polymer. The Examiner's assertion is not correct, and this becomes especially clear when considering the significant guidance provided in the application concerning the objected-to elements and the nature of the invention.

Guidance Concerning First and Second Organic Solvents

Significant guidance is provided concerning the first and second organic solvents. As noted above, the cosolvent system, including the nature of and the criteria for selecting the first and second solvents, is thoroughly discussed in the application at, *inter alia*, page 4, line 9 through page 6, line 8; page 11, line 20 through page 17, line 2; and page 19, line1 through page 22, line 14. The tests shown in the Examples section of the application provide additional guidance.

At page 5 line 16 through page 6, line 8, in the Summary of Invention section, it is specifically noted that mutually soluble organic solvents preferred for inclusion in the cosolvent

system will depend upon the specific composition and/or other characteristics of the insulin-containing particles to be manufactured. Preferred cosolvent systems are then specifically discussed for use when making pure insulin particles (DMSO as the first organic solvent and a lower alcohol as the second organic solvent) and for making multi-component particles including a biocompatible polymer (lower alcohol as the first organic solvent and methylene chloride as the second organic solvent). The invention, however, is not limited to these preferred embodiments.

At page 12, line 13 through page 13, line 16, it is disclosed that the first and second organic solvents are mutually soluble at the temperature and pressure conditions of contacting with the compressed anti-solvent fluid, and are preferably also mutually soluble at ambient conditions. Furthermore, it is disclosed that for most applications, the first organic solvent will be a significantly better solvent for insulin and another organic solvent (e.g., the second organic solvent) will be a significantly worse solvent for the insulin. It is also disclosed that for most applications, the cosolvent system is preferably richer in the second organic solvent than the first organic solvent, and typical and preferred weight ratios for the second organic solvent to the first organic solvent are discussed.

At page 14, line 3 through page 16, line 7 there is a discussion specifically concerning the cosolvent system with respect to one preferred embodiment when making pure insulin particles. Among other things, it is disclosed that it is preferred that the second organic solvent be more readily extractable by the anti-solvent feed than the first organic solvent and that organic solvents with higher volatilities will tend to be more extractable. These general criteria for selecting first and second organic solvents are then followed by examples of some specific first and second organic solvents for use with this embodiment. Specific examples of some preferred second organic solvents disclosed for use with this embodiment include alcohols, ketones, aldehydes, nitriles and halogenated hydrocarbons, and particularly lower molecular weight members of these groups that are readily extractable by the anti-solvent feed. Disclosed as being particularly preferred for use as the second organic solvent in this embodiment are lower molecular weight alcohols, with even more preferred attributes of such alcohols being further described. Specific examples of some preferred first organic solvents disclosed for use with this embodiment include DMSO and DMFA.

At page 19, line1 through page 20, line 8 there is a discussion specifically concerning the cosolvent system with respect to another preferred embodiment when making multi-component particles including insulin and a biocompatible polymer. Among other things, it is disclosed that the first organic solvent is typically a better solvent for the insulin, that the second organic solvent is typically a better solvent for the biocompatible polymer, and that the first organic solvent is typically a poor solvent for the biocompatible polymer. Moreover, the second organic solvent is typically a nonpolar solvent and the first organic solvent is typically a polar solvent. At least an order of magnitude difference often exists in the solubilities of the first and second organic solvents for insulin and the biocompatible polymer, respectively. These general criteria for selecting first and second organic solvents are then supplemented by examples of some specific materials for the first and second organic solvents disclosed for use with this embodiment. Specific examples of some preferred first organic solvents disclosed for use with this embodiment include DMSO, DMFA and alcohols (more preferably lower molecular weight alcohols). Specific examples of some preferred second organic solvents for use with this embodiment include methylene chloride, formaldehyde, dioxolane, chloroform, benzene, ethyl ether, toluene, xylene, 1,3-dioxane and tetrahydrofuran. Moreover, at page 20, lines 7-17, examples of some preferred second organic solvents are disclosed specifically correlated for use with various different biocompatible polymers.

Moreover, the Examples show a total of 37 tests to provide further guidance to assist in understanding first and second organic solvent selection. The tests include both comparative tests and tests showing several combinations of first and second organic solvents and different relative concentrations and operating conditions, and both for preparing pure insulin particles and multi-component particles that include a biocompatible polymer.

Guidance Concerning Compressed Anti-Solvent Fluid

Significant guidance is provided concerning the compressed anti-solvent fluid. The compressed anti-solvent fluid is discussed in the application, *inter alia*, at page 9, line 15 through page 11, line 14. There, it is specifically disclosed that an important consideration for the compressed anti-solvent fluid is that it should preferably have a strong solvating power for solvents in the feed solution (e.g., the first and second organic solvents). Furthermore, it is preferred that the compressed anti-solvent fluid be such that insulin is essentially insoluble in the

compressed anti-solvent fluid. Examples of 19 specific materials for potential use as the compressed anti-solvent fluid are presented at page 9, line 20 through page 10, line 3. Moreover, at page 10, line 7 through page 11 line 14, guidelines are presented concerning temperature and pressure properties of the compressed anti-solvent fluid during the contacting step. These temperature and pressure guidelines are presented in terms of the dimensionless quantities of reduced temperature and reduced pressure, so as to be generally applicable to different compressed anti-solvent fluids. Specific temperature and pressure values are discussed for the most preferred compressed anti-solvent fluid, carbon dioxide. The 37 tests shown in the Examples section of the application provide additional information concerning properties of the compressed anti-solvent fluid through specific demonstrations.

Guidance Concerning Biocompatible Polymer

In one embodiment, claimed in Claims 20-48, the method of the invention involves making a multi-component particulate product including both insulin and a biocompatible polymer. The application provides significant guidance concerning the recited biocompatible polymer.

A discussion concerning the biocompatible polymer is presented in the application, *inter alia*, at page 16, line 19 through page 18, line 16. The polymer must be biocompatible. Also, the polymer is typically biodegradable and hydrophobic. Also, preferred molecular weight ranges are provided (2 kDa – 300 kDa, with 20 kDa - 150 kDa being more preferred). Moreover, a substantial list of exemplary biocompatible polymers is presented at page 17, lines 4-17. The tests shown in the Examples section provide additional guidance, even though those tests use only various molecular weights of poly(l-lactic acid).

Guidance Concerning Separation of Particles

The application specification provides significant guidance concerning separation of the particulate product from the compressed anti-solvent fluid. For example, at page 11, lines 15-19, it is disclosed that some suitable separation techniques include sedimentation, filtration and centrifuging, all well known solid/fluid separation techniques. Moreover, in the tests shown in the Example section of the application, further guidance is provided through the use of two specific filters is discussed (polyvinylidene fluoride and polytetrafluorethylene filters).

Claims Not Limited to Preferred Embodiments or by Working Examples

Importantly, it is noted that all of Claims 1-48 involve a method for making an insulin-containing particulate product from known starting materials. The invention as claimed in Claims 1-48 does not involve a new chemical compound or manufacture of any new chemical compound. Rather the invention involves a technique for incorporating insulin, and optionally a biocompatible polymer, into a particulate product form. Furthermore, the method does not depend upon the occurrence of unpredictable chemical reactions. The nature of the method of the invention is precipitation of insulin, optionally together with other components, from a feed solution through interaction between the solvent and a compressed anti-solvent fluid. It is well known that claims to an invention need not necessarily limited to preferred embodiments. It certainly is the case that the method of the invention may be easier to operate in some circumstances relative to other circumstances, and that insulin-containing particles produced may be better for a particular administration application when prepared according to one set of operating parameters relative to another set of operating parameters. But protection of the invention should be limited to cover only embodiments that work best.

Moreover, the Examiner's position appears to require that working examples be provided for every possible combination of first and second organic solvents in the cosolvent system, compressed antisolvent fluid, separation technique, and biocompatible polymer (in the case of claims directed to the multi-component particulates). This approach is not proper, and has been clearly rejected by courts in addressing the enablement standard.

With respect to working examples, MPEP §2164.02 specifically states: "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." MPEP §2164.02 then cites to the case of *In Re Borkowski*, 422 F.2d 904, 164 USPQ 642 (CCPA 1970), concerning the proper standard for considering working in relation to enablement determinations. A copy of *Borkowski* is enclosed.

In *Borkowski*, the claims at issue concerned a method of preparing oxygenated hydrocarbon including a step requiring chlorination of a vapor phase hydrocarbon feed. The examiner in *Borkowski* had rejected the claims, stating that the description "is not such that it would enable one skilled in the art to practice the present invention, particularly with reference to the chlorination step," with the examiner specifically mentioning "relative amounts of

hydrocarbon" and "magnitude of reaction times" as parameters which should have been more fully disclosed. [*Borkowski* at p. 907.] The examiner in *Borkowski* further stated, in rejecting claims, that "moreover, the conditions are obviously not the same for methane as they are for the myriad of other hydrocarbons contemplated and urged to be suitable for use in the instant process." [*Borkowski* at p.908.] The Patent Office Board of Appeals affirmed the rejection and stated that an "exemplary correlation" of process variables should necessarily be provided.

The CCPA in *Borkowski* interpreted the "exemplary correlation" requirement as a requirement for working examples and clearly rejected the proposition, stating:

> [A]s we have stated in a number of opinions, [citations omitted] a specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Here, while it may be that an "exemplary correlation" of parameters such as times of reaction and rates of reactant feed and product removal would give the worker in the art some useful information and provide a "jumping off place," we see no basis for concluding that without such information the worker in the art would not be enabled by the specification to practice the invention, i.e., to "balance" the several reactions involved in the applicants' process. The "few hours" experimentation mentioned by the examiner certainly would not seem to be an undue amount of time considering the nature of the claimed invention. We therefore cannot agree with the reasons given by the examiner and the board for concluding that applicants' specification does not comply with §112. [*Borkowski* at pp. 908].

The examiner in *Borkowski* had also rejected the claims based on undue breadth and indefiniteness in recitation of "hydrocarbon reactant." The examiner's reasons being stated as follows:

> This term ["hydrocarbon"] encompasses an almost limitless number of compounds, and hence, is *not adequately supported by the somewhat limited disclosure*. The salient *absence of a representative example* for the various types of hydrocarbons alleged to be suitable for use in the instant process further render[s] the *support for the breadth of the claims on appeal inadequate*. [*Borkowski* at pp. 908-909, emphasis as added by the court.]

The court in *Borkowski* rejected the examiner's position, stating:

> [W]e do not agree either that claims 7-10 are rendered "unduly broad" or "indefinite" by the term "hydrocarbon" or that a "representative example for the various types of hydrocarbons" is needed. As applicants point out, claims 7-10 are limited to hydrocarbons with are in a vapor phase at the reaction temperature and thus do not call for just any hydrocarbon. Moreover, there is no magical relation between the number of representative examples and the breadth of the claims: the number and variety of examples are irrelevant if the disclosure is "enabling" and sets forth the "best mode contemplated." [*Borkowski* at pp. 909-910.]

As in *Borkowski*, the applicant here is not required to set forth every conceivable combination of specific conditions and materials required for practicing the method as claimed. In that regard, it is specifically noted that Claim 1 does not include all organic solvents, and compressed anti-solvent fluids and Claim 20 does not include all biocompatible polymers. Rather Claim 1 is limited to specific first and second organic solvents and compressed anti-solvent fluid combinations in a method for processing insulin to make insulin-containing particulates. Specifically, Claim 1 is limited such that the first and second organic solvents are mutually soluble and that the compressed anti-solvent fluid is contactable with the first and second organic solvents (in the cosolvent system) to precipitate insulin-containing products. The structure of the claims is such that only specific combinations of the first and second organic solvents and compressed anti-solvent fluids are covered that are operable in the recited method to produce the insulin-containing particles. Likewise, in Claim 20, the polymer is limited to biocompatible polymers that are processable with the feed solution to prepare multi-phase particles including both the biocompatible polymer and the insulin. The claims are, therefore, limited to only specific combinations of first and second organic solvents, compressed anti-solvent fluids and, for Claim 20, biocompatible polymers that are processable as recited in the claims to make insulin-containing particles.

Nature of Invention

The claims to the present invention should not be unduly restricted relative to the nature of the invention. In that regard, reference is made to the case of In Re Fuetterrer, 319 F.2d 259, 138 USPQ 217 (CCPA 1963), a copy of which is enclosed. In Fueterrer, the claims at issue recited a rubber stock for producing tire treads including "a mixture of a non-adhesive protein and a carbohydrate which mixture is substantially insoluble in cold water" and including an

"inorganic salt that is capable of holding a mixture of said carbohydrate and protein in colloidal suspension in water." [Fuetterrer at p. 260.] The Patent Office rejected the claims, and the Patent Office Board of Appeals affirmed the rejection on grounds that the claims were too broadly drawn because only four of the large number of possible inorganic salts were disclosed in the application. The CCPA overturned the rejection stating that the specification need not set forth all salts which could operate in the claimed combination. The court in Fuetterrer rejected the Patent Office's assertion that identifying usable salts would involve undue experimentation and specifically stated:

> Applicant's invention is the *combination* claimed and not the discovery that certain inorganic salts have colloidal suspending properties. We see nothing in the patent law which requires applicant to discover which of all those salts have such properties and which will function properly in his combination. The invention description clearly indicates that any organic salt which has such properties is usable in his combination. If others in the future discover that inorganic salts additional to those enumerated do have such properties, it is clear applicant will have no control over them per se, and equally clear his claims should not be so restricted that they can be avoided merely by using some inorganic salt not named by applicant in his disclosure. The only "undue burden" which is apparent to us in the instant case is that which the patent office has attempted to place on the applicant. The patent office would require him to do research on "literally thousands" of inorganic salts and determine which of these are suitable for incorporation into his claimed combination, apparently forgetting that he has not invented, and is not claiming colloidal suspending agents but tire tread stock composed of a combination of rubber and other ingredients. [Fueterrer at p. 265, emphasis as in original.]

Likewise, the instant application does not claim organic solvents, anti-solvent fluids, or biocompatible polymers, per se. Rather, the instant application claims a method for making an insulin-containing particulate product involving processing insulin, and in some embodiments also a biocompatible polymer, involving the use of first and second organic solvents and a compressed anti-solvent fluid, the method being useful for converting insulin to a particulate form, with or without other components. Consistent with the holding of the CCPA in Fueterrer, claims to the present invention should not be unduly restricted in a manner to permit others to easily circumvent the claims simply because the applicant has not identified every specific combination of first and second organic solvents, compressed anti-solvent fluid and, in the case of Claim 20, biocompatible polymer. Again, the claims are not directed to organic solvents, anti-

solvent fluids or biocompatible polymers, per se, but rather only to a method for processing these materials along with insulin to make an insulin-containing particulate product.

No Undue Experimentation

MPEP § 2164.06 notes that the quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether undue experimentation is required to make and use the invention. A considerable amount of testing is permissible if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. As discussed above, considerable guidance is provided in the application concerning use of the claimed method of the invention, including substantial guidance concerning the first and second organic solvents, the compressed anti-solvent fluid, processing conditions of temperature and pressure, separation of particles and biocompatible polymers. This significant guidance alone, as noted in MPEP § 2164.06, is sufficient to demonstrate enablement, particularly given the nature of the invention and the fact that the claims cover only operative embodiments, as discussed above.

Additionally, any testing that would be required with the present invention is not extensive, and in any event would not be considered to be undue. For example, any proposed combination of first and second organic solvents can be tested for mutual miscibility simply by mixing them together to see if they form a single phase or separate into multiple phases. The suitability of the compressed anti-solvent fluid for interacting with the first and second organic solvents can be tested by simply contacting the compressed anti-solvent fluid with the first and second organic solvent mixture to see if the compressed anti-solvent readily invades and dissolves the first and second organic solvents. Insulin could then be mixed with the first and organic solvents, optionally with any desired biocompatible polymer, and the first and second organic solvents could be contacted with the compressed anti-solvent fluid to test for precipitation of insulin-containing particles under the desired contacting conditions. These types of tests are representative of the types of tests that would routinely be run by someone skilled in the art contemplating making insulin-containing particles according to the present invention. The Examiner's assertions of "exhaustive research" and the like are unsubstantiated when considering the significant guidance provided in the specification or the nature of the invention.

Based on the foregoing, it is respectfully submitted that that the rejection of Claims 1-48 under 35 U.S.C. §112, first paragraph, should be withdrawn.

Enclosed is petition for a three month extension of time to respond pursuant to 37 C.F.R. §1.136(a) and a check in the amount of $460 for extension fees under 37 C.F.R. §1.17, based on small entity status. No other fees are believed to be due with this communication. If, however, any fees are due, please debit such fees to Deposit Account No. 50-1419. Credit any over payments to Deposit Account No. 50-1419. Should the filing of this response require an additional extension of time under 37 C.F.R. § 1.136(a), such extension is requested and any deficiency in payment of extension fees should be debited to Deposit Account No. 50-1419.

The application is believed to be in condition for allowance and allowance of all pending claims is earnestly requested. If the Examiner believes that it would be helpful to discuss any of the amendments or remarks presented, or to discuss possible Examiner amendments, the Examiner is respectfully invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method for making an insulin-containing particulate product, the method comprising:

contacting an insulin-containing feed solution with a compressed anti-solvent fluid to precipitate insulin-containing particles, the feed solution including the insulin in a cosolvent system, the cosolvent system including at least a first organic solvent and a second organic solvent that are mutually soluble, the first organic solvent and the second organic solvent not being the same; and

separating the insulin-containing particles from the anti-solvent fluid.

14. (Amended) The method of claim 1, wherein the feed solution is ~~substantially~~ free of ~~amphiphillic~~ amphiphilic materials that improve solubility of the insulin in the feed solution through hydrophobic ion pairing with the insulin.

18. (Amended) The method of Claim 1, wherein the cosolvent system is ~~substantially~~ free of water.

23. (Amended) The method of claim 20, wherein the first organic solvent is ~~substantially~~ miscible with water and the second organic solvent is ~~substantially~~ immiscible with water.

35. (Amended) The method of claim 34, wherein the second solution is prepared by ~~first~~ dissolving the acid in~~with~~ the second organic solvent and then dissolving the insulin in the second organic solvent.

38. (Amended) The method of claim 20, wherein both of the first organic solvent and the second organic solvent are ~~substantially~~ soluble in the compressed anti-solvent fluid.

46. (Amended) The method of claim 20, wherein ~~the contacting step is conducted under conditions so that~~ the multi-component particles have a degree of encapsulation of the insulin by the polymer of greater than about 50 percent.

47. (Amended) The method of claim 20, wherein the ~~contacting step is conducted under conditions so that~~ the multi-component particles have a degree of encapsulation of the insulin by the polymer of greater than about 70 percent.

48. (Amended) The method of claim 20, wherein the biocompatible polymer includes a poly(lactic acid).